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1 *The above-entitled matter came on for hearing on Thursday,*
2 *January 12, 2012, commencing at 1:40 p.m., at the U.S. Patent and*
3 *Trademark Office, 600 Dulany Street, 9th Floor, Alexandria, Virginia,*
4 *before Stanley Ross, Notary Public.*

5
6 THE USHER: Calendar No. 53, Appeal No. 2011-002275, Mr.
7 North.

8 JUDGE MILLS: Mr. North, as a preliminary matter, would you
9 have a business card for the Court Reporter?

10 MR. NORTH: Certainly.

11 JUDGE MILLS: Could you also introduce your colleague?

12 MR. NORTH: I will. My name is Christopher North. I'm
13 representing Appellants in this matter. With me is Mr. Yon DeSummer,
14 representative for subject matter.

15 JUDGE MILLS: We are familiar with the record in your case.
16 You have 20 minutes and you can begin when you're ready.

17 I believe we understand your arguments fully with regard to the
18 112, so we don't need to hear any additional argument on that.

19 MR. NORTH: Very well. As I was preparing for this
20 proceeding, it occurred to me that it might help to take a step back and put
21 the invention in the scientific and historical context, and with your
22 permission, I would use the white board to illustrate some of that. Is that
23 possible?

24 JUDGE LEBOVITZ: I don't know if there is a white board.

25 JUDGE MILLS: There is a white board.

26 JUDGE LEBOVITZ: Sorry.

1 JUDGE MILLS: Help yourself.

2 MR. NORTH: The invention here is kind of a Swiss Army
3 knife of molecular manipulation. Just to put it in a scientific context,
4 remember molecular biology tells us that inside a plant cell, you have a
5 nucleus, and inside the nucleus, you have the genetic material which is
6 comprised of DNA.

7 That DNA contains all the instructions that the cell needs to
8 perform all its functions. Those instructions are for the most part carried out
9 by the cell creating proteins to do the jobs.

10 That happens by a mechanism in which the DNA is copied first
11 to an mRNA molecule.

12 JUDGE LEBOVITZ: We're very familiar with --

13 MR. NORTH: You are all molecular biologists? All right.

14 JUDGE LEBOVITZ: Either we are or we have dealt with it,
15 and we don't need detailed background.

16 MR. NORTH: I'll go quickly to this part. The mRNA comes
17 outside the nucleus and that is processed through machinery that creates the
18 protein in the cell.

19 The invention here is a way of interrupting this,
20 post-transcriptional gene silencing.

21 JUDGE LEBOVITZ: Right. How does the double stranded
22 RNA work to silence the gene?

23 MR. NORTH: Let me get to that, because I do want to put the
24 prior art in perspective.

25 At the time this invention was being made, there were a few
26 things known about gene silencing. It was known that you could use

1 antisense, you could introduce that into a cell that corresponded to a target
2 mRNA. You could have gene silencing. That was a fairly sporadic event. It
3 only happened maybe 7 to 15 percent of the time according to Exhibit 9.

4 Another phenomenon that was recognized was you could put in
5 genes which could create a lot of plus strand RNA, strands of RNA which
6 corresponded with the sequence of the mRNA would also create silencing.

7 The Examiner in this case cited three references, Flavell, Stam,
8 and Metzloff, all of which exemplify the efforts of scientists at the time to
9 understand these two phenomena.

10 Our inventors had a hypothesis and that hypothesis was that a
11 triggering mechanism could be triggered by introducing into the cell a
12 double stranded RNA.

13 JUDGE LEOVITZ: Is there any explanation of how the
14 double stranded is different than the way they postulated in terms of
15 degradation?

16 MR. NORTH: What was never done with any of these methods
17 was create a construct that would simultaneously produce whole percent in
18 the antisense strand and produce silencing.

19 At the time this application was filed, the process -- this can be
20 known as "RNA interference" -- the mechanism wasn't known.

21 Examples 2 through 5 of the specification show a series of
22 experiments in which they created these constructs. These experiments went
23 on over years because they were dealing with plants, and you have to wait a
24 season in order to get your plant from your seedlings, and then if you want
25 another generation, you have to wait again.

1 They created the constructs first to create this module, and they
2 saw whereas these would generate silencing maybe 7 to 10 percent of the
3 time, this would generate silencing almost 50 percent of the time. It was a
4 huge increase in efficiency.

5 They then did experiments in which they put these individually
6 into plants and re-crossed them to demonstrate that the effect was really
7 caused when these two things were present simultaneously, and because it
8 was one or the other individually or --

9 JUDGE LEBOVITZ: They put the sense in one plant and the
10 antisense in another?

11 MR. NORTH: They didn't get the silencing. They combined
12 those and they did get silencing.

13 JUDGE LEBOVITZ: Let's jump to the prior art, the second
14 rejection, which is over Flavell and a bunch of other references.

15 The closest prior art looked to me to be Stam, because that one
16 for sure talked about inverted repeat. Inverted repeats are for a hairpin.

17 MR. NORTH: That's not necessarily true. Unfortunately, the
18 Stam reference doesn't give you the whole context of what Stam was talking
19 about when talking about inverted repeats.

20 We did present a declaration by Dr. Metzlauff who is one of
21 those authors, and gives some explanation.

22 To sort of step outside of that for a second, the inverted repeats
23 that Stam is talking about, he was talking about a sense strand, putting into
24 the plant cells -- they use a mechanism called "T-DNA," and basically you
25 put the gene you want to put in a plant cell into this T-DNA. That's a vector
26 that gets the gene incorporated into the plant's genome.

1 When it gets incorporated into the plant's genome, sometimes
2 you get one, sometimes you get two, sometimes you get eight. They can
3 face opposite directions or together.

4 The thing that happens is that these are still -- even though they
5 are inverted repeats -- these are individual genes. This is a gene with a
6 promoter and a terminator. Even though they are inverted, they don't
7 necessarily produce hairpin RNA.

8 It's a bit misleading to read that inverted repeat as if it would
9 necessarily produce a hairpin RNA.

10 That is why --

11 JUDGE LEBOVITZ: I didn't see that in the declaration by
12 Dr. --

13 MR. NORTH: No, I don't think he addressed that particular
14 question. I apologize.

15 JUDGE LEBOVITZ: It felt as if he was deliberately not
16 discussing the thing that popped out when you read the reference, and that's
17 discussing inverted repeats.

18 When we get a case, we look at it independently. We are not
19 siding with the Examiner. We are not siding with an Appellant. We're
20 reading the record and we are trying to make a decision.

21 We read a reference and we see "inverted repeats," whether the
22 Examiner recognized it or played up on it, it just seems that's not a good idea
23 because it gets passed down on the credibility of the declarant, the declarant
24 really not addressing everything in the reference.

25 Now we understand your point and it's pretty clear from reading
26 it, but it's just something you should be aware of, that we are reading this

1 very independently, and when it looks like the declarant is not hitting a point
2 that's the most obvious point to hit, he becomes less credible.

3 MR. NORTH: I think maybe it was less obvious to him. With
4 his knowledge, he would think those inverted repeats wouldn't produce a
5 hairpin so why address it.

6 JUDGE LEBOVITZ: Possibly.

7 MR. NORTH: One of the rejections the Examiner did cite --

8 JUDGE LEBOVITZ: You're saying there were complete
9 copies of the gene in there. They were oriented inversely of each other, and
10 there's no evidence there in the reference that mRNA was made from it, and
11 not only that, they don't discuss it in the reference.

12 MR. NORTH: Yes. Even though he mentions "inverted
13 repeats" and says there was some silencing, he had no idea what part of the
14 inverted repeats would have been a triggering event.

15 There would be no reason to take from that that this is the
16 molecule you need to make in the plant cell.

17 JUDGE PRATS: If I could interject, I believe on page eight of
18 the Metzlauff declaration, it does address the standard. He doesn't seem to
19 explain why he disagrees.

20 We don't have any direct evidence that these structures are
21 absent, but we don't have any evidence they were necessarily there; correct?

22 The declarant mentions, and this is more for the benefit of the
23 panel, that these structures are not within a single gene as contemplated by
24 the application.

25 He's saying again, we're sort of hypothesizing they are there,
26 but there is no direct evidence; correct?

1 MR. NORTH: I think that's true. I think the basis for that
2 statement is his understanding of the T-DNA, what that process would have
3 been.

4 JUDGE LEBOVITZ: With the prior art, let's assume for a
5 minute Stam, what would have been the reason to have put introns onto the
6 hairpin in the prior art? The double stranded RNA, whatever it was.

7 MR. NORTH: As you can see from Fire, Fire's experiments in
8 worms were using the molecule that looked like that. That's what they were
9 injecting into worms. They do, however, have some disclosures in there that
10 says you can do it in plants, although they had no evidence, and they have a
11 disclosure in there that says it can be a single cell complimentary molecule.

12 They have no disclosure in there of putting in anything else but
13 the sense and the antisense.

14 There's no disclosure in Fire. The Examiner cited three
15 references that do talk about introns, and let me address those for a moment.

16 Lusky and SchiednerSchiedner can be taken together. Those
17 both describe a adenoviral vector. Adenoviral vectors are viral vectors used
18 in animals to cause the production, not suppression, of a gene.

19 Lusky only teaches -- the only disclosure with regard to introns
20 in Lusky is the genes you can include in her vector may or may not be
21 introns in the same manner that animal genes may or may not include
22 introns.

23 That doesn't provide you any reason to add an intron to a
24 molecule like this.

25 The actual subject matter of the case now has this, where -- it's
26 a double stranded and it has an intron.

1 That doesn't provide you any reason to do that in this molecule,
2 which is designed to suppress gene expression in plants.

3 Schiedner is also talking about demi-viral vectors. Demi-viral
4 vectors, when you wish to produce them in cells, it's helpful if the size of the
5 genome that you are encapsulating in the viral capsule matches the size of
6 the viral capsule.

7 In one line, he describes using an intron as a stopper in order to
8 produce or have the ability to make these --

9 JUDGE LEBOVITZ: Which reference was that again?

10 MR. NORTH: That's Schiedner. Brown, the third reference, is
11 a little bit different. That is in a plant cell, but Brown is describing a method
12 to enhance the production of proteins. Brown is describing an intron which
13 they have found is useful to include in the untranslated leader sequence, and
14 when that happens, for reasons unknown, you get an increased production of
15 the protein which is encouraging your transgene.

16 That is the exact opposite of what we are attempting to do here,
17 and there is nothing in Brown that would give you a reason for including
18 that intron in a vector in which you have sense and antisense for the purpose
19 of suppressing the expression of a protein.

20 Even if Fire stands, I don't believe you get from Fire to the
21 present invention. There are secondary indicia of non-obviousness that I
22 would like to address.

23 JUDGE LEBOVITZ: None of those were introduced by
24 declaration, were they? Go ahead.

25 One argument you had was articles showed greater stability, but
26 usually when we go with secondary consideration like that, normally there

1 has to be some evidence that it was unexpected to the person of ordinary
2 skill in the art.

3 MR. NORTH: Let me take from the evidence that appears.
4 These methods are producing suppression at about 7-10-15 percent,
5 according to Exhibit 9, Table 1, Smith compared these kinds of constructs,
6 sense and antisense constructs alone produced suppression of about 7 to 15.

7 A construct which had a random stopper sequence, there was a
8 hairpin with a random stopper sequence that produced suppression of about
9 60 percent of the time.

10 A construct as described in the claims produced suppression 96
11 to 100 percent of the time.

12 We did introduce the publication by Smith. There is also a
13 publication in Exhibit 10 by Wesley, which compares these constructs to
14 other similar constructs, and gives the same kind of results.

15 There are Exhibits 10 through 18 that all demonstrate the
16 following of the publication of the results in Smith, which is essentially a
17 publication in Nature of the experiment that was conducted as Example 6 of
18 our specification.

19 The art has essentially adopted this technique almost
20 exclusively, and all those papers are an example, referencing Smith as the
21 source.

22 JUDGE LEBOVITZ: Smith was the Nature 2000?

23 MR. NORTH: Smith was a Nature 2000 paper. I

24 JUDGE LEBOVITZ: September 2000.

25 MR. NORTH: In the first column on page 320, it referred to
26 the fact that the results they obtained with the intron were "amazing."

1 JUDGE LEBOVITZ: Where is that?

2 MR. NORTH: That is --

3 JUDGE LEBOVITZ: "Amazingly." Okay.

4 MR. NORTH: It was unheard of success, compared to the old
5 antisense, and even the results originally gotten.

6 JUDGE LEBOVITZ: Even if we don't find that Fire -- the
7 declaration isn't good enough to overcome Fire, you still have evidence here
8 of non-obviousness?

9 MR. NORTH: I think so. I think both the results -- you can
10 also find these results -- one of our declarants referred to -- Mark DeBlock's
11 declaration describes the fact that he became aware of the results which are
12 in Example 6 of the specification because of the association between his
13 group and the inventors.

14 When he became aware of those results, he immediately took
15 up the use of introns in his own construct.

16 There is declaration evidence that shows persons of skill in the
17 art saw this and immediately adopted it, in addition to the publications we
18 have presented.

19 Schofield, reading the specification, said he understood the
20 inclusion of an intron significantly enhanced the effectiveness of the
21 construct.

22 That appears on page six of his declaration, paragraph 27.

23 JUDGE LEBOVITZ: Okay. I don't have any more questions.

24 MR. NORTH: I would like to address for a moment the
25 sufficiency of the 131 declaration because you have been hinting at that.

1 JUDGE LEBOVITZ: Okay. Let me just raise one of the issues
2 that I saw, and that was the examples were around 500 and 700 base errors,
3 but the claims go down to 20.

4 Under Stiller and Stencil, you should either show as much as
5 the reference shows, which in this case would be 20 because that's what Fire
6 showed, or whatever you show would make the rest of the claim obvious.

7 The fact that you show 500 up here and you don't show the
8 lower region, and there's no explanation as to why the lower region would
9 have been obvious from the upper region, I think that was the Examiner's
10 objection.

11 MR. NORTH: The first point I would make, the Examiner's
12 objection, as I understood it, went to the question -- she was suggesting that
13 the declaration needed to support the claims in a genus species sense.

14 That's clearly not the law. You have identified the law in
15 saying what you need to show is as much as the reference shows.

16 JUDGE LEBOVITZ: Right.

17 MR. NORTH: We would point out that if you look at the actual
18 work that Fire did, the table which describes all of the constructs they tested,
19 those constructs are all in the hundreds.

20 While their specification and their claims recite 25, what they
21 demonstrated was potentially the same as the examples in our declarations.

22 The other point you raised is you correctly identified the fact
23 that in what you have done would have rendered what was shown, assuming
24 what Fire showed is everything that he speculated, I think the fact that he did
25 that despite having examples in the hundreds, combined with the Examiner's

1 own citation of Baracchini -- Baracchini is one of the references the
2 Examiner cited in conjunction with Fire.

3 Baracchini was cited for the proposition that it would be
4 obvious to use nucleotides. Baracchini shows an antisense, using antisense
5 at 20.

6 I think it would be inconsistent to suggest that it wouldn't have
7 been obvious to go all the way down to 20 when that paper was cited for that
8 purpose.

9 I think Fire and Baracchini together show persons of ordinary
10 skill in the art understood that the lower limit for these kinds of phenomena
11 was around 20 bases. Baracchini understood it. Fire understood it.

12 That's not something that would have been doubted by a person
13 of ordinary skill in the art.

14 JUDGE LEBOVITZ: Okay. That makes sense. I have one
15 more issue, and that is the claim also requires that you get a hairpin, an
16 artificial hairpin.

17 Is there any evidence in the declaration that the inventors
18 recognized that an artificial hairpin was being formed?

19 I guess question number two, more importantly, is that
20 necessary for a 131? I know in diligence, you would need to show that.

21 I'm just wondering about that issue.

22 MR. NORTH: To be precise, the claim says wherein the RNA
23 is capable of forming an artificial hairpin. I don't think there is any doubt in
24 the 131 declaration that the authors intended and created it for the purpose of
25 being capable of forming an artificial hairpin.

1 JUDGE LEBOVITZ: It does seem that way. I'm just asking,
2 that you have to have some recognition that they recognize that the construct
3 was an artificial hairpin at whatever date you're alleging conception, and I'm
4 wondering whether that argument is necessary for a 131.

5 MR. NORTH: My understanding is the necessity of a 131 is
6 that you show at least what the reference shows.

7 JUDGE LEBOVITZ: Right.

8 MR. NORTH: The question of whether or not that actually has
9 to match the claim is a different question.

10 There is case law, I believe, that says the 131 and the
11 interference standards are not coextensive.

12 On the other hand, I don't want to back away from my belief
13 that they knew what they were creating when they did it, and --

14 JUDGE LEBOVITZ: I'm not saying -- right.

15 MR. NORTH: They even pointed out on page 151 -- I think
16 there may be a drawing.

17 JUDGE LEBOVITZ: There may be.

18 MR. NORTH: In paragraph six -- for example, on page 151 of
19 the notebook --

20 JUDGE LEBOVITZ: Exhibit 1 or Exhibit 2?

21 MR. NORTH: Which one is that in? Exhibit 1 of the 131
22 declaration. You can see at the top of the page it says "Creation of a PDY
23 mRNA hairpin."

24 There is no question that's what they were intending and
25 expected.

26 JUDGE LEBOVITZ: Right. I was just wondering aloud.

1 JUDGE MILLS: Do you have any concluding remarks you
2 would like to make?

3 MR. NORTH: No, since you did not wish to hear about the 112
4 issue.

5 JUDGE LEBOVITZ: I apologize. It's just a pet peeve of mine,
6 if they don't sort of address head on what's in the reference, and often times,
7 the Examiner is not on the right issue.

8 MR. NORTH: It's a good practice. Thank you very much.

9 JUDGE MILLS: Okay. Thank you.

10 (Whereupon, at 2:00 p.m., the proceedings were concluded.)

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